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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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| (51) International Patent Classification ⁷ : A61K 38/55, A61P 29/00 | A1 | (11) International Publication Number: WO 00/41716 (43) International Publication Date: 20 July 2000 (20.07.00) |
| (21) International Application Number: PCT/SE00/00051 (22) International Filing Date: 13 January 2000 (13.01.00) (30) Priority Data: 9900070-5 13 January 1999 (13.01.99) SE (71) Applicant (for all designated States except US): AS-TRAZENECA AB [SE/SE]; S-151 85 Södertälje (SE). (72) Inventor; and (75) Inventor/Applicant (for US only): KIRK, Ian [GB/GB]; Astra Charnwood, Bakewell Road, Loughborough, Leics. LE11 5RH (GB). (74) Agent: ASTRAZENECA AB; Intellectual Property, Patents, S-151 85 Södertälje (SE). | | (81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published With international search report. With amended claims. |
| (54) Title: NEW USE OF MELAGATRAN (57) Abstract According to the invention there is provided the use of melagatran, or a pharmaceutically acceptable derivative or prodrug thereof, in the manufacture of a medicament for the treatment of inflammation. | | |

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NEW USE OF MELAGATRAN

Field of the Invention

- 5 This invention relates to a new use of the low molecular weight thrombin inhibitor, melagatran.

Introduction

- 10 Inflammation is a localised protective response elicited by injury or destruction of tissues, which serves to destroy, dilute or sequester both the injurious agent and the injured tissue.

- Inflammation may result from physical trauma, infection, some chronic
15 diseases (e.g. psoriasis and autoimmune diseases, such as rheumatoid arthritis) and/or chemical and/or physiological reactions to external stimuli (e.g. as part of an allergic response). A complex series of events may be involved, in which inflammatory mediators increase blood flow and dilation of local blood vessels, resulting in redness and heat, the exudation
20 of fluids, often resulting in localised swelling, leukocytic migration into the inflamed area, and pain.

- Current local and systemic treatments of inflammation, which treatments are employed typically when inflammation is an inappropriate response
25 (e.g. in the treatment of autoimmune diseases), or is uncomfortable and/or inconvenient, include the administration of *inter alia* non-steroidal anti-inflammatory agents (NSAIDs), opioid analgesics and corticosteroids.

Prior Art

International patent application WO 94/29336 discloses a group of compounds that are useful as inhibitors of serine proteases, such as thrombin and/or kininogenases, such as kallikrein. The thrombin-inhibiting compounds are thus indicated as anticoagulants, and the kininogenase-inhibiting compounds as antiinflammatory agents.

One of the thrombin inhibiting compounds that is specifically disclosed in WO 94/29336 is $\text{HOOC-CH}_2\text{-(R)Cgl-Aze-Pab-H}$, which is also known as melagatran (see Example 1 of WO 94/29336, and the list of abbreviations in this document). The use of melagatran in the inhibition of kininogenases, and therefore in the treatment of inflammation, is neither mentioned nor suggested.

Disclosure of the Invention

We have now found, surprisingly, that melagatran elicits a notable antiinflammatory effect, for example as described below, and may thus be used to treat inflammation in preferably mammalian, and especially human, patients.

According to a first aspect of the invention there is provided the use of melagatran, or a pharmaceutically acceptable derivative or prodrug thereof, in the manufacture of a medicament for the treatment of inflammation.

The term "inflammation" will be understood by those skilled in the art to include any condition characterised by a localised protective response

elicited by injury or destruction of tissues resulting from any of the causes mentioned hereinbefore, and which is manifest by heat, swelling, pain, redness, dilation of blood vessels and/or increased blood flow, invasion of the affected area by white blood cells, loss of function and/or any other
5 symptoms known to be associated with the inflammatory condition. The term will thus be understood to include *inter alia* acute, chronic, ulcerative, specific, allergic and necrotic inflammation, as well as all other forms of inflammation known to those skilled in the art.

10 Melagatran, and derivatives and prodrugs thereof, may thus be used in the direct treatment of inflammation resulting from injury, from viral or bacterial infection, or from a disease characterised by inflammation as one of its symptoms. Such diseases include autoimmune diseases, such as rheumatoid arthritis, psoriasis, allergy, asthma, rhinitis, pancreatitis,
15 urticaria and inflammatory bowel syndrome.

However, melagatran, and derivatives and prodrugs thereof, are preferably used in the treatment of inflammation in patients with, or at risk of, a disease in which inhibition of thrombin is desired or required
20 (see, for example, those listed in international patent application WO 97/23499), such as a thrombotic disease. Although the treatment may be of patients whose inflammatory and thrombotic diseases are unrelated, we prefer that the treatment is of a patient with a thrombotic disease in which inflammation plays a part in triggering coagulation. For example,
25 inflammation may arise in blood vessel walls due to the presence and/or the action of microbes and/or the agents released thereby, physical damage, atherosclerotic lesions and other inflammation-inducing agents. It is preferred that melagatran, and derivatives and prodrugs thereof, are

used in the treatment of inflammation in patients having, or at risk of having, a thrombus.

For the avoidance of doubt, as used herein, the term "treatment" includes
5 the therapeutic and/or prophylactic treatment of inflammation.

"Pharmaceutically acceptable derivatives" includes salts (e.g. pharmaceutically acceptable non-toxic organic or inorganic acid addition salts) and solvates. The term "prodrug" of melagatran includes any
10 compound that, following oral or parenteral administration, is metabolised *in vivo* to form melagatran (see, for example, international patent application WO 97/23499). Preferred prodrugs are those of the formula $R^1O_2C-CH_2-(R)Cgl-Aze-Pab-OH$ (see the list of abbreviations in WO 97/23499), wherein R^1 represents linear or branched C_{1-6} alkyl (e.g. C_{1-4}
15 alkyl, especially methyl, propyl and, particularly, ethyl) and the OH group replaces one of the amidino hydrogens in Pab.

Melagatran, and derivatives and prodrugs thereof, may be administered for systemic delivery to the site of inflammation, or may be administered
20 for delivery directly (locally) to that site, using appropriate means of administration that are known to the skilled person.

Thus, in accordance with the invention, melagatran, and derivatives and prodrugs thereof, may be administered orally, intravenously,
25 subcutaneously, buccally, rectally, dermally, nasally, tracheally, bronchially, topically, by any other parenteral route, or *via* inhalation, in the form of a pharmaceutical preparation comprising the active ingredient in a pharmaceutically acceptable dosage form. Depending on the

disorder, and the patient, to be treated, as well as the route of administration, the compositions may be administered at varying doses.

Preferred modes of delivery are systemic. For melagatran and derivatives thereof, preferred modes of administration are parenteral, more preferably intravenous, and especially subcutaneous. For prodrugs of melagatran, preferred modes of administration are oral.

In the therapeutic treatment of mammals, and especially humans, melagatran and derivatives and prodrugs thereof may be administered alone, but will generally be administered as a pharmaceutical formulation in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier, which may be selected with due regard to the intended route of administration and standard pharmaceutical practice. The preparation of suitable formulations for use in administering melagatran, derivatives and prodrugs thereof is described in the literature, for example as described in *inter alia* international patent applications WO 94/29336, WO 96/14084, WO 96/16671, WO 97/23499, WO 97/39770, WO 97/45138, WO 98/16252, WO 99/27912 and WO 99/27913, the disclosures in which documents are hereby incorporated by reference. Otherwise, the preparation of suitable formulations may be achieved non-inventively by the skilled person using routine techniques.

The amounts of melagatran, or derivative or prodrug thereof, in the formulation will depend on the severity of the condition, and on the patient, to be treated, as well as the compound(s) which is/are employed, but may be determined non-inventively by the skilled person.

According to a further aspect of the invention there is provided a pharmaceutical formulation for use in the treatment of inflammation comprising an effective amount of melagatran or a pharmaceutically acceptable derivative or prodrug thereof, in admixture with a
5 pharmaceutically acceptable adjuvant, diluent or carrier.

Melagatran, and derivatives and prodrugs thereof, may also be combined with other therapeutic agents that are useful in the treatment of inflammation (e.g. NSAIDs, corticosteroids and analgesics), and/or other
10 therapeutic agents that are useful in the treatment of a disease characterised by inflammation as one of its symptoms. Melagatran, and derivatives and prodrugs thereof, may also be combined with other therapeutic agents which, when administered, are known to give rise to inflammation as a side-effect. When melagatran, and derivatives and
15 prodrugs thereof, are "combined" with other therapeutic agents in this way, the active ingredients may be administered together in the same formulation, or administered separately (simultaneously or sequentially) in different formulations.

20 Suitable doses of melagatran, prodrugs and derivatives thereof, in the therapeutic and/or prophylactic treatment of mammalian, especially human, patients are those which give a mean plasma concentration in the range 0.01 to 5 $\mu\text{mol/L}$. In any event, the physician, or the skilled person, will be able to determine the actual dosage which will be most
25 suitable for an individual patient, which is likely to vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case; there can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

The skilled person will also appreciate that melagatran, or a derivative or prodrug thereof, may be administered in an appropriate dose on an "as required" basis (i.e. as needed or desired).

5

According to a further aspect of the invention there is provided a method of treating inflammation which comprises administering a therapeutically effective amount of melagatran, or a pharmaceutically acceptable derivative or prodrug thereof, to a patient in need of such treatment.

10

The use and method described herein may have the advantage that, in the treatment of inflammation, melagatran and derivatives and prodrugs thereof may not possess disadvantages of known antiinflammatory agents. The use and method described herein may also have the advantage that melagatran and derivatives and prodrugs thereof may be more efficacious than, be less toxic than, have a broader range of activity than, be more potent than, produce fewer side effects than, be more easily absorbed than, or that they may have other useful pharmacological properties over, compounds known in the prior art for the treatment of inflammation.

20

The invention is illustrated, but in no way limited, by the following example.

Example 1

25

Groups of five male Charles River CD rats in the weight range 180 to 240 g were used. On their arrival, rats were housed in controlled environment rooms and fed a standard diet for at least one week before use.

Rats were starved overnight before the test, although water was given *ad libitum*. A mark was made on the ankle joint of each rat, the day before the test, to indicate where the foot volume was to be measured.

- 5 Compounds were made up in the appropriate vehicle for dosing *via* either the subcutaneous (s.c.), intravenous (i.v.) or oral (p.o.) routes. Melagatran was dosed in water (20 $\mu\text{mol/kg}$) when given p.o., and in saline, and in cyclodextrin (40%), when given s.c. (0.7 to 2 $\mu\text{mol/kg}$). Drugs were administered in a dose volume of 5 mL/kg body weight for
10 p.o. dosing or 1 to 2 mL/kg body weight for s.c. dosing. Control rats received the equivalent volume of vehicle.

A 1% solution of carrageenan in saline was prepared the day prior to the test. The carrageenan was suspended in saline and stirred vigorously on a
15 magnetic stirrer for one hour. It was then stored at 4°C until required. Thirty minutes after dosing, each rat was injected s.c. in the plantar region of the left hind foot with 0.1 mL of 1% carrageenan.

To reduce both discomfort to the rat and variability in the test, rats were
20 housed on wood chip bedding in solid bottom cages. The rats had access to a solution of 5% glucose throughout the duration of the test.

Foot volumes were measured using a water plethysmograph, the output being displayed using a digital voltmeter and recorded using a Mac-Lab
25 program. The plethysmograph was calibrated using blocks of 2 mL and 4 mL mass before the first, and after the last, measurement at each time point.

Foot volumes were measured before dosing and up to 6 hours after the sub-plantar injection of carrageenan. The increase in foot volume for each rat was calculated using the difference between the individual foot volume at time zero, and at the various time points. The inhibition afforded by a treatment was expressed as a percentage inhibition of the mean absolute increase in foot volume in treated animals compared to control animals. Indomethacin at 10 mg/kg p.o. was always included as an internal standard. If indomethacin gave less than 30% inhibition at 4 h then the test was considered invalid.

10

A number of standard compounds were tested and the results shown in Table 1.

Table 1

| Compound | Dose (route) | % Inhibition after sub-plantar injection | |
|---------------|-------------------|--|---------------|
| | | 2 hours after | 4 hours after |
| Indomethacin | 10 mg/kg (p.o.) | 43 | 50 |
| Dexamethasone | 0.3 mg/kg (p.o.) | 51 | 96 |
| Dexamethasone | 0.03 mg/kg (p.o.) | 47 | 74 |
| Ibuprofen | 10 mg/kg (p.o.) | 22 | 26 |

15

When melagatran was administered orally (20 μ mol/kg) in water 30 minutes prior to the sub-plantar injection of carrageenan, it was ineffective in inhibiting paw oedema at up to 6 h post dosing. When given s.c. in cyclodextrin (2 μ mol/kg) a 29% inhibition of the oedema was observed at 1 hour (Table 2).

20

Table 2

| Compound | Dose | % Inhibition after | | | |
|--------------|------------------------|--------------------|---------|---------|---------|
| | | 1 hour | 2 hours | 3 hours | 4 hours |
| Indomethacin | 10 mg/kg (p.o.) | -5 | 50 | 39 | 12 |
| Melagatran | 20 μ mol/kg (p.o.) | 14 | 17 | -14 | -2 |
| Melagatran | 2 μ mol/kg (s.c.) | 29 | 13 | 3 | 13 |

When melagatran was administered in saline at a dose of 24 μ mol/kg s.c., a 39% inhibition of the oedema was observed after 1 h (Table 3).

5

Table 3

| Compound | Dose | % Inhibition after | | | |
|--------------|-----------------------|--------------------|---------|---------|---------|
| | | 1 hour | 2 hours | 3 hours | 4 hours |
| Indomethacin | 10 mg/kg (p.o.) | 15 | 2 | 29 | 18 |
| Melagatran | 2 μ mol/kg (s.c.) | 39 | 8 | 2 | -8 |

This finding was investigated further, with melagatran being administered in saline at doses of 0.7, 1.4 and 2 μ mol/kg s.c., 30 minutes prior to a sub-plantar injection of carrageenan, with paw oedema being measured at 1, 1.5, 2 and 3 hour time points. The results are shown in Table 4.

Table 4

| Compound | Dose | % Inhibition after | | | |
|------------|-------------------------|--------------------|-----------|---------|---------|
| | | 1 hour | 1.5 hours | 2 hours | 3 hours |
| Melagatran | 0.7 μ mol/kg (s.c.) | 39 | -1 | 9 | 16 |
| Melagatran | 1.4 μ mol/kg (s.c.) | 65 | 40 | 5 | 7 |
| Melagatran | 2.0 μ mol/kg (s.c.) | 76 | 41 | 17 | 19 |

Due to the short duration of this experiment, indomethacin controls were not included.

It can be seen clearly that melagatran inhibited paw oedema in both a dose
5 dependent, and time dependent, manner.

Claims

1. The use of melagatran, or a pharmaceutically acceptable derivative or prodrug thereof, in the manufacture of a medicament for the treatment
5 of inflammation.
2. The use of melagatran, or a pharmaceutically acceptable derivative or prodrug thereof, in the manufacture of an antiinflammatory medicament.
10
3. A method of treatment of inflammation which comprises administering a therapeutically effective amount of melagatran, or a pharmaceutically acceptable derivative or prodrug thereof, to a patient in need of such treatment.
15
4. A pharmaceutical formulation for use in the treatment of inflammation comprising an effective amount of melagatran, or a pharmaceutically acceptable derivative or prodrug thereof.
- 20 5. Use of melagatran, or a pharmaceutically acceptable derivative or prodrug thereof, for the treatment of inflammation by administering melagatran, or a pharmaceutically acceptable derivative or prodrug thereof, to a patient.
- 25 6. The use of melagatran, or a pharmaceutically acceptable derivative or prodrug thereof, in the treatment of inflammation.
7. A use, method or formulation as claimed in any one of Claims 1 to 6 (as appropriate), wherein the treatment is of inflammation in patients

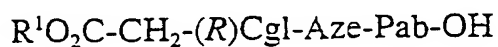
with, or at risk of, a disease in which inhibition of thrombin is desired or required.

8. A use, method or formulation as claimed in Claim 7, wherein the
5 disease is one in which inflammation plays a part in triggering
coagulation.

9. A use, method or formulation as claimed in Claim 7 or Claim 8,
wherein the patient has, or is at risk of, a thrombus.

10

10. A use, method or formulation as claimed in any one of the
preceding claims, wherein the prodrug is the formula



wherein R^1 represents linear or branched C_{1-6} alkyl and the OH group
15 replaces one of the amidino hydrogens in Pab.

11. A use, method or formulation as claimed in Claim 10, wherein R^1
represents methyl, ethyl or propyl.

AMENDED CLAIMS

[received by the International Bureau on 13 June 2000 (13.06.00);
new claims 12-16 added ; remaining claims unchanged ; (3 pages)]

1. The use of melagatran, or a pharmaceutically acceptable derivative
or prodrug thereof, in the manufacture of a medicament for the treatment
5 of inflammation.
2. The use of melagatran, or a pharmaceutically acceptable derivative
or prodrug thereof, in the manufacture of an antiinflammatory
medicament.
- 10 3. A method of treatment of inflammation which comprises
administering a therapeutically effective amount of melagatran, or a
pharmaceutically acceptable derivative or prodrug thereof, to a patient in
need of such treatment.
- 15 4. A pharmaceutical formulation for use in the treatment of
inflammation comprising an effective amount of melagatran, or a
pharmaceutically acceptable derivative or prodrug thereof.
- 20 5. Use of melagatran, or a pharmaceutically acceptable derivative or
prodrug thereof, for the treatment of inflammation by administering
melagatran, or a pharmaceutically acceptable derivative or prodrug
thereof, to a patient.
- 25 6. The use of melagatran, or a pharmaceutically acceptable derivative
or prodrug thereof, in the treatment of inflammation.
7. A use, method or formulation as claimed in any one of Claims 1 to
6 (as appropriate), wherein the treatment is of inflammation in patients

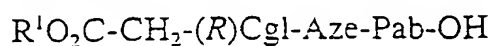
with, or at risk of, a disease in which inhibition of thrombin is desired or required.

8. A use, method or formulation as claimed in Claim 7, wherein the
5 disease is one in which inflammation plays a part in triggering coagulation.

9. A use, method or formulation as claimed in Claim 7 or Claim 8, wherein the patient has, or is at risk of, a thrombus.

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10. A use, method or formulation as claimed in any one of the preceding claims, wherein the prodrug is the formula



wherein R^1 represents linear or branched C_{1-6} alkyl and the OH group
15 replaces one of the amidino hydrogens in Pab.

11. A use, method or formulation as claimed in Claim 10, wherein R^1 represents methyl, ethyl or propyl.

20 12. A drug combination comprising melagatran, or a pharmaceutically acceptable derivative or prodrug thereof, and another therapeutic agent that is useful in the treatment of inflammation.

13. A drug combination comprising melagatran, or a pharmaceutically
25 acceptable derivative or prodrug thereof, and another therapeutic agent that is useful in the treatment of a disease characterised by inflammation as one of its symptoms.

14. A combination as claimed in Claim 12 or Claim 13, wherein the other therapeutic agent is an NSAID, a corticosteroid or an analgesic.

15. A combination as claimed in any one of Claims 12 to 14 wherein
5 the melagatran, derivative or prodrug thereof is combined with the other therapeutic agent together in the same formulation.

16. A combination as claimed in any one of Claims 12 to 14 wherein
the melagatran, derivative or prodrug thereof, and the other therapeutic
10 agent, are administered separately (simultaneously or sequentially), in different formulations.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 00/00051

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 38/55, A61P 29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, REG. CAPLUS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|--|-----------------------|
| X | WO 9739770 A1 (ASTRA AKTIEBOLAG), 30 October 1997 (30.10.97) | 4 |
| | -- | |
| A | WO 9725994 A1 (HANSSON, HANS-ARNE), 24 July 1997 (24.07.97) | 1-11 |
| | -- ----- | |

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

14 April 2000

Date of mailing of the international search report

10-05-2000

Name and mailing address of the ISA/

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE00/00051

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 5-11
because they relate to subject matter not required to be searched by this Authority, namely:
see next sheet
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).:

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application. as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE00/00051

Claims 5-11 relate to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT

Information on patent family members

02/12/99

International application No.

PCT/SE 00/00051

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---------------------|----------------------------|---------------------|
| WO 9739770 A1 | 30/10/97 | AU 2719597 A | 12/11/97 |
| | | AU 7716496 A | 19/06/97 |
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